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Stages of disease severity and factors that affect the health status of patients with chronic obstructive pulmonary disease

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Background: We hypothesized that the factors which may influence health status would differ in patients at different disease stages of chronic obstructive pulmonary disease (COPD). The present study investigated how impairments in health status were distributed in male patients at each disease stage according to the British Thoracic Society (BTS) guidelines, and analysed the contribution of the clinical indices, the dyspnoea rating and the psychological status to the health status of patients at the three disease stages of COPD.

Methods: A total of 218 consecutive male patients with stable COPD were recruited from our outpatient clinic. All eligible patients completed pulmonary function testing, progressive cycle ergometry, a dyspnoea rating [Medical Research Council (MRC) dyspnoea scale], an assessment of their anxiety and depression [Hospital Anxiety and Depression Scale (HADS)], and an assessment of their health status [the St. George's Respiratory Questionnaire (SGRQ)]. The patients were categorized into three groups: mild COPD with a FEV_1 at 60–79% of the predicted value, moderate COPD at 40–59% of the predicted value, and severe COPD at below 40% of the predicted value.

Results: Twenty-five patients (11%) had mild COPD, 72 patients (33%) had moderate COPD, and 121 patients (56%) had severe COPD. Significant differences were observed for the total score and for three components on the SGRQ among patients at the three stages (one-way ANOVA, $P<0{\cdot}05$). The scores for the total SGRQ and for the activity component were significantly higher for patients with severe COPD than for patients with moderate COPD [Fisher's least-significant-difference (LSD) method, $P<0{\cdot}05$], and also significantly higher for moderate COPD patients than for mild COPD patients. The maximal oxygen uptake ($\dot{V}O_2$ max) correlated significantly with the total SGRQ score in the mild patients [Pearson's correlation coefficient (r) $=-0{\cdot}67$], but not in the moderate or severe patients. The MRC dyspnoea scale had strong correlations with the SGRQ in all patient groups ($r=0{\cdot}53\simeq0{\cdot}70$). Anxiety and depression on the HADS showed moderate correlations with the SGRQ score in the mild and severe patients ($r=0{\cdot}51\simeq0{\cdot}57$). Multiple regression analysis showed that in patients with mild COPD, the MRC and $\dot{V}O_2$ max accounted for the total score on the SGRQ. Anxiety on the HADS plus the MRC scale accounted for the total score on the SGRQ in patients with moderate COPD, and anxiety on the HADS, the MRC scale and the FEV_1 significantly influenced the SGRQ severe COPD patients.

Conclusions: The disease staging proposed by the BTS guidelines can separate patients with COPD according to impairments in their health status. Furthermore, the factors that influence health status differed in patients at the three disease stages. Our findings support the boundaries used in disease staging and some recommendations from the BTS guidelines.

Key words: chronic obstructive pulmonary disease; health status; staging of disease severity.

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Introduction

Patients with COPD can be functionally divided into three stages based on their severity of airflow limitation (1). This standardized categorization can facilitate prognostication, clinical recommendations and health source planning in patients with COPD (1). The percentage of the predicted FEV_1 is used as the basis for the staging systems proposed by the British Thoracic Society (BTS) (1), as well as by the American Thoracic Society (ATS) (2) and the European Respiratory Society (3). Although the precise boundaries chosen are rather arbitrary and differ between each set of guidelines, the following severity ranges were established in the BTS guidelines: mild COPD with a FEV_1 at 60–79% of the predicted value, moderate COPD at 40–59% of the predicted value, and severe COPD at below 40% of the predicted value.

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When evaluating patients with COPD, the health status or health-related quality of life has been recognized as one of the more important outcomes in clinical studies (4,5), and the BTS guidelines emphasized that improving the quality of life is one of their goals. The relationship between disease staging and health status warrants further investigation. For example, Ferrer *et al*. showed that the worse disease stage defined by the ATS presented with the worse health status (6); they also pointed out that patients at ATS stage I had a poorer health status than reference groups of healthy people. However, the relationship between the BTS guidelines and the health status has yet to be examined.

The major factors that influence the health status of patients with COPD are dyspnoea and their psychological status, whereas physiological parameters such as their exercise capacity and FEV_1 generally do not contribute very much to impairments in health status (7). However, it remains unclear whether the same factors affect patients with an early stage of COPD *vs*. severe disease stage. We hypothesized that the factors which may influence the health status would differ in patients at the three different disease stages. In the present cross-sectional study, we investigated how impairments in the health status were distributed in male COPD patients at each disease stage as defined by the BTS guidelines. We also evaluated correlations between their health status and other clinical variables, and analysed the contribution of pulmonary function, exercise capacity, the dyspnoea rating and the psychological status to the health status of COPD patients at the three disease stages. The health status was assessed with a disease-specific instrument, the St. George's Respiratory Questionnaire (SGRQ) (8).

Methods

PATIENTS

Patients with stable COPD as defined by the BTS guidelines (1) were recruited from our outpatient clinic. All of the patients had at least 6 months of outpatient management before entry in order to avoid substantial changes in subjective parameters induced by any new medical interventions (9). The entry criteria for this study were: (i) a maximal FEV_1/vital capacity (VC) ratio of less than 0·7 and value of FEV_1 of less than 80% of the predicted for all measurements made over the prior 6 months; (ii) a smoking history of more than 20 pack-years; (iii) no history suggestive of asthma; (iv) no exacerbations of their airflow limitation over the preceding 6 weeks and (v) no changes in treatment regimen over the preceding 4 weeks. All eligible patients finished the following examinations on the same day, including pulmonary function testing, progressive cycle ergometer testing, an assessment of their health status and an assessment of their dyspnoea, anxiety and depression.

PULMONARY FUNCTION TESTS

FEV_1 and forced vital capacity (FVC) were assessed after the inhalation of bronchodilators was withheld for at least 12 h. All spirometric flow–volume curves were recorded according to the method described in the ATS 1994 update (10). The predicted values for the FEV_1 and FVC were calculated based on the Japan Society of Chest Diseases' proposal (11). The residual volume (RV) was measured by the closed-circuit helium method, and the transfer coefficient for carbon monoxide (T_{LCO}) was measured using the single-breath technique (CHESTAC-65V, Chest, Tokyo, Japan). Patients on long-term domiciliary oxygen therapy (LTOT) were advised to stop inhaling their oxygen at least 12 h prior to their visits.

SYMPTOM-LIMITED PROGRESSIVE CYCLE ERGOMETER EXERCISE TEST

A progressive exercise test to a symptom-limited maximum was performed using an electrically braked cycle ergometer (Corival WLP-400, Lode, Groningen, The Netherlands) at 60 min after the inhalation of bronchodilators, as described by Ikeda *et al*. (12). The workload was increased automatically, and the patients maintained a pedalling frequency above 40 cycles min^{-1} throughout the test. The exercise data were recorded with an automated exercise testing system (Desktop Diagnostics/CPX, Medical Graphic Corporation, St. Paul, U.S.A.). At the end of each exercise test, the maximal oxygen uptake ($\dot{V}O_2$) was calculated. All exercise tests were performed by the same researcher (M.T.), who did not have any prior knowledge of the results of the pulmonary function tests.

ASSESSMENT OF THE HEALTH STATUS, DYSPNOEA, ANXIETY AND DEPRESSION

Health status was assessed by the Japanese version of the SGRQ (8), which has previously been validated (7). The SGRQ is divided into three components: symptoms (distress caused by specific respiratory symptoms), activity (physical activities that cause or are limited by breathlessness) and impacts (social and psychological effects of the disease). The total score for the SGRQ was also calculated following the procedures outlined by its developers. The SGRQ scores range from 0 to 100, with a zero score indicating no impairment in health status. Dyspnoea was evaluated with the Japanese version of the MRC dyspnoea scale, which consists of a five-point grade (13). The Japanese version of the Hospital Anxiety and Depression Scale (HADS) (14) was used to evaluate the patients' anxiety and depression status. The HADS consists of 14 items, seven of which score for anxiety and seven of which score for depression. It was scored in accordance with the methods proposed by it original author. The theoretical scores for anxiety and depression on the HADS range from 0 to 21; a score from 8 to 10 denotes borderline anxiety or depression and a score over 11 denotes clinical anxiety or depression. The SGRQ, MRC scale, and HADS were

self-administered in booklet form. One of the authors (M.T.) checked all of the patients' answers in order to avoid possible missing items.

STATISTICAL ANALYSIS

All results are expressed as means ± SD. The distribution of all variables approximated a normal distribution, and thus parametric tests were used throughout the present study. Relationships, between two sets of data were analysed using Pearson's product-moment correlation test. A P-value of less than 0·01 was considered to be statistically significant. Differences in the physiological values (RV/TLC, T_{LCO}, and maximal $\dot{V}O_2$) and the SGRQ scores among the subgroups were compared by an analysis of variance (ANOVA), and statistical significance was established $P<0·05$. Multiple pairwise comparisons were made with Fisher's least-significant-difference (LSD) method, with the overall α level set at 0·05. Forward and backward stepwise multiple regression analysis was performed to identify those variables which could predict the health status (15). Variables that were judged to be important for COPD were used as independent variables for the regression analysis. The variables were the FEV_1 for airflow limitation, the RV/TLC ratio for hyperinflation, the T_{LCO} % predicted for gas exchange, the $\dot{V}O_2$ max for exercise capacity, the MRC scale for dyspnoea, and anxiety on the HADS for psychological status. The dependent variable for this statistical model was the total score from the SGRQ.

All analyses were performed with the statistical program Statview Version 4·1 (Abacus, Concepts, Berkeley, CA, U.S.A.).

Results

Patient characteristics are summarized in Table 1. A total of 218 consecutive male patients with COPD were evaluated and were categorized into three stages of COPD based on the BTS guidelines. Twenty-five patients (11%) had mild COPD, 72 patients (33%) had moderate COPD, and 121 patients (56%) had severe COPD. Forty-six patients were current smokers. Two hundred and eleven patients (97%) were treated with inhalation of both β-agonists and anti-cholinergic agents. In addition to the inhaled agents, oral theophylline (300 ~ 800 mg day^{-1}) was administered in 22 patients (10%), and oral prednisolone (2·5 ~ 10 mg day^{-1}) in 10 patients (5%). One hundred and four patients (48%) were also treated with high doses (1600 ~ 2400 mg day^{-1}) of inhaled beclomethasone dipropionate. Five patients received no medication, and seven patients were managed with LTOT.

Significant differences were observed for the RV/TLC and the $\dot{V}O_2$ max (one-way ANOVA, $P<0·05$) The $\dot{V}O_2$ max was significantly lower in patients with severe COPD than in patients with moderate COPD (Fisher's LSD method, $P<0·05$; indicated by † in Table 1). The $\dot{V}O_2$ max was also significantly lower for moderate COPD patients than for mild COPD patients (Fisher's LSD method, $P<0·05$; indicated by * in Table 1). No significant differences in the T_{LCO} were recognized among the three groups.

Significant differences were observed for the total score and for three components on the SGRQ (one-way ANOVA, $P<0·05$), which are shown in Table 2. The total score and the activity component on the SGRQ were significantly higher in patients with severe COPD than in patients with moderate COPD (Fisher's LSD method, $P<0·05$; indicated by † in Table 2), and were also significantly higher for moderate COPD patients than for mild COPD patients (Fisher's LSD method, $P<0·05$; indicated by * in Table 2). For the symptoms and impacts components of the SGRQ, the score in the severe COPD patients was significantly higher than in mild COPD patients, but was not significantly different from that in moderate COPD patients. No significant differences in the HADS scores were recognized among the three groups based on disease severity.

There were different patterns in the relationship between the SGRQ score and the other clinical variables among the

TABLE 1. Characteristics of 218 consecutive male patients with COPD

	Mild COPD	Moderate COPD	Severe COPD
n	25	72	121
Age (years)	69 (9)	69 (7)	68 (6)
FEV_1(l)	1·89 (0·25)	1·33 (0·21)	0·75 (0·20)
FEV_1(% pred)	70·2 (4·7)	50·0 (6·1)	28·7 (7·3)
RV/TLC (%)	40·6 (13·1)	43·2 (10·7)	53·9 (9·8)*†
T_{LCO} (% pred)	72·4 (15·9)	69·6 (20·8)	63·9 (19·7)
$\dot{V}O_2$ max (ml min^{-1})	1019 (323)	895 (270)*	740 (243)*†

The data represent mean (SD).
T_{LCO}: transfer factor for carbon monoxide; max: $\dot{V}O_2$ maximal oxygen uptake. Mild COPD: FEV_1 60–79% of the predicted value; moderate COPD: FEV_1 40–59% of the predicted value; severe COPD: FEV_1 below 40% of the predicted value.
*Significant differences in the values were observed for patients with mild COPD (Fisher's least-significant-difference method, $P<0·05$).
†Significant differences in the values of those with moderate COPD (Fisher's least-significant-difference method, $P<0·05$).

TABLE 2. The scores for the health status, dyspnoea rating and psychological status in patients at the three disease stages of COPD

	Mild COPD	Moderate COPD	Severe COPD
n	25	72	121
SGRQ			
Symptoms	43·7 (22·1)	48·0 (18·8)	54·7 (19·2)*†
Activity	24·9 (23·9)	34·8 (21·1)*	46·8 (18·4)*†
Impacts	15·5 (15·5)	22·4 (16·3)	26·1 (15·9)*†
Total score	24·2 (17·6)	31·8 (16·2)*	39·0 (15·0)*†
MRC scale	1·5 (0·96)	1·7 (0·8)	2·3 (0·8)*†
HADS			
Anxiety	3·6 (2·7)	3·8 (3·2)	4·5 (3·2)
Depression	4·2 (3·1)	4·5 (3·2)	4·7 (3·7)

The data represent means (SD).
SGRQ: the St George's Respiratory Questionnaire (SGRQ); MRC: Medical Research Council dyspnoea scale; HADS: Hospital Anxiety and Depression Scale.
*Significant differences in the scores were observed for patients with mild COPD (Fisher's least-significant-difference method, $P<0{\cdot}05$).
†Significant differences in the scores of those with moderate COPD (Fisher's least-significant-difference method, $P<0{\cdot}05$).

TABLE 3. Pearson's correlation coefficients between the SGRQ and other clinical variables in 218 consecutive male patients with COPD

	Total score on the SGRQ		
	Mild COPD	Moderate COPD	Severe COPD
n	25	72	121
FEV_1 (l)	−0·34 [0·098]	−0·12 [0·338]	−0·24 [0·010]
RV/TLC (%)	−0·17 [0·431]	0·40 [0·702]	0·14 [0·137]
T_{LCO} (% pred)	−0·32 [0·044]	−0·29 [0·028]	−0·20 [0·0131]
$\dot{V}O_2$ max (ml min^{-1})	−0·67 [<0·001]	−0·20 [0·097]	−0·39 [<0·001]
MRC scale	0·70 [<0·001]	0·62 [<0·001]	0·53 [<0·001]
HADS			
Anxiety	0·50 [0·009]	0·31 [0·009]	0·51 [<0·001]
Depression	0·53 [0·008]	0·35 [0·003]	0·57 [<0·001]

For a definition of the abbreviations, see the footnotes of Tables 1 and 2.
Numbers in the square parentheses represent *P*-values.

three disease stages (Table 3). With respect to physiological parameters, FEV_1 had low correlation with the SGRQ score in patients with severe COPD [Pearson's correlation coefficient (r) = −0·24], but there were no significant correlations in patients with mild or moderate COPD. The $\dot{V}O_2$ max was significantly correlated with the total SGRQ score in the mild COPD patients ($r=-0{\cdot}67$), but not in the moderate or severe patients. The MRC dyspnoea scale had strong correlations with the SGRQ score in all patient groups ($r=0{\cdot}53\sim0{\cdot}70$). Anxiety and depression on the HADS showed moderate correlations with the SGRQ score in the mild and severe COPD patients ($r=0{\cdot}51\sim0{\cdot}57$).

Results of the stepwise multiple regression analyses are shown in Table 4. In patients with mild COPD, the MRC scale and $\dot{V}O_2$ max accounted for 63% of the variance in the total score on the SGRQ. Anxiety on the HADS and the MRC scale accounted for 43% of the total SGRQ score in patients with moderate COPD. With respect to patients with severe COPD, Anxiety on the HADS, the MRC scale and the FEV_1 all significantly influenced the SGRQ.

Discussion

The present study showed that the disease staging proposed by the BTS guidelines could stratify male COPD patients

TABLE 4. Results of the stepwise multiple regression analysis in the cross-sectional study

	Total score for the SGRQ		
	Mild COPD ($n=25$)	Moderate COPD ($n=72$)	Severe COPD ($n=121$)
Independent variables			
FEV_1 (l)	—	—	0·07 [−0·16]
RV/TLC (%)	—	—	—
T_{LCO} (% pred)	—	—	—
$\dot{V}O_2$ max (ml min^{-1})	0·29 [−0·43]	—	—
MRC scale	0·34 [0·49]	0·32 [0·59]	0·20 [0·41]
Anxiety on HADS	—	0·11 [0·21]	0·20 [0·41]
Cumulative R^2	0·63	0·43	0·47

All of the values listed above represent a coefficient of multiple determination (R^2).
Numbers in the square parentheses represent standardized regression coefficients.
For a definition of the abbreviations, see the footnotes of Tables 1 and 2.
Missing values indicate that the independent variables were not statistically significant.

according to varying degrees of impairment in their health status. We found that the health status of patients with mild to severe COPD had different patterns with respect to its correlations with physiological parameters, and that the factors that influenced the impairments in the health status of COPD patients differed between the three disease stages. In terms of improving health status, it may be reasonable to change medical interventions and therapeutic goals in accordance with the disease stage.

To our knowledge, the present study is the first report on the relationship between health status and disease staging proposed by the BTS guidelines. This study demonstrated that patients in the worst disease stage had the worst scores on the total SGRQ and on the activity component; the scores for the symptoms and impacts components also showed the same tendency. In this regard, the boundaries chosen for the BTS staging may be appropriate with respect to the health status. However, the precise boundaries chosen for the staging are rather arbitrary: the BTS guidelines selected 80%, 60% and 40% as the cut-off points for the predicted FEV_1 values (1), whereas the ATS guidelines are set at 80%, 50% and 35% (2). Ferrer *et al.* reported that patients in the worst disease stage defined by the ATS guidelines had the worst health status as evaluated by the SGRQ and a generic instrument, the Nottingham Health Profile (6).

In patients with mild COPD, the exercise capacity as evaluated by the maximal oxygen consumption correlated significantly with and influenced the total score on the SGRQ; thus, their mildly decreased exercise capacity appeared to affect their health status. Our findings support the recommendations of the BTS guidelines that patients with mild disease should be encouraged to continue with all of their usual activities.

Anxiety and dyspnoea played important roles in the health status of patients with moderate to severe COPD. Our results are consistent with the previous finding that anxiety was associated with an impaired health status (16). The multiple regression analysis showed that anxiety influenced the health status more in severe COPD patients than in moderate COPD patients, although there was no significant difference in the anxiety score on the HADS between these two groups. It is conceivable that anxiety and dyspnoea, both of which correlate with each other, may impact the health status strongly, especially in patients with severe COPD. In this regard, psychotherapy for patients with severe COPD may be considered as one of the therapeutic options. For example, in their pilot study, Eiser *et al.* demonstrated that cognitive and behavioural psychotherapy produced an improvement in exercise capacity (17).

The present study confirmed that dyspnoea is one of the main determinants of health status, and had moderate-to-strong correlations with impairments in the health status of patients with mild-to-severe COPD, as previously reported (7,18). Since even mild breathlessness can impair the health status of patients with mild COPD, medical interventions for relieving dyspnoea such as inhaled bronchodilators may be justified in the early stages of COPD.

We should mention the limitations of the present study. Our study included only males, since we experienced difficulty in recruiting a sufficient number of female patients with COPD. Therefore, any generalization of our results to women with COPD may be unwarranted. Second, since we recruited only stable patients from our outpatient clinic who were able to perform a progressive cycle ergometer test, some of the more symptomatic patients may have been excluded. We also experienced difficulty in enrolling patients with mild COPD, mainly because they presented with very few symptoms and thus were reluctant to visit our clinic in a university setting. Since the cumulative coefficients of determination in the regression analysis were not high, the indices used in this study may not be adequate,

and unknown factors remain which may influence the health status of patients with COPD.

In conclusion, the disease staging proposed by the BTS guidelines was able to stratify patients with COPD according to impairments in their health status. Furthermore, the factors that influenced the health status differed in patients at the three different disease stages. Our findings support the boundaries of the disease staging and some of the recommendations proposed by the BTS guidelines.

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